FROM: R. KHOSLA Ranjan Khosla 6/III/2002 DATE: MARCH 6, 2002

TO: G. MARINI, M. SHOEMAKER, M. ASCHENBRENNER, N. GRETHE, W. STAGER

C.C. M. QUIGLEY, B. LEROY, R. NUSRAT, J. PAKULSKI

SUBJECT: STUDY HMR3647A/ 3014 (TREAT)
EVALUATION FOR SCIENTIFIC MISCONDUCT / US SITE #1129
MEETING MINUTES

Attendees

A. Cisneros (Sr. CRA, TCC, PPD)
M. Edwards (Project Manager, TCC, PPD)
J. Reynolds (CRA, TCC, PPD)
J. Lasley (Director TCC, PPD)
R. McCormick, (Vice President, Quality Management Systems, PPD)
A. Wear (Site Management CRA, TCC, PPD)
N. Grethe (Study Manager, Aventis)
W. Stager (Statistician, Aventis)
M. Shoemaker (GCP-QA, Aventis)
G. Marini (GCP-QA, Aventis)
M. Aschenbrenner (GCP-QA, Aventis)
R. Khosla (GCP-QA, Aventis)

Background

Anne Kirkman-Campbell, MD [Investigator No. 1129] is the highest enroller in the TREAT Study with 407 subjects enrolled. PPD CRAs Christiane Hammond and Jerry Ferguson monitored this site on November 29, 2001. The CRAs monitored three of the 65 subjects enrolled at the time of that visit. Ranjan Khosla (GCP-QA, Aventis) had conducted an audit at this site on January 17-18, 2002. At the time of the audit the site had enrolled 327 subjects. The auditor reviewed all 327 ICFs, the essential document binder, drug accountability and the charts of subjects 060, 080, 100, 140, 180, 191, 200, 220, 240, and 280. The Study Coordinator entering the date for the PI and/or the subjects on the ICFs; the PI entering the date for the person obtaining the consent and/or the subjects; partial compliance to the CFR 312.62 requirement that the case history of each individual shall document that informed consent was obtained prior to participation in the study; and other problems pertaining to informed consent were some of the significant issues. During the exit interview, the auditor confirmed that the PI and the Study Coordinator were not aware of the complete definition and reporting requirements of Adverse Events of Special Interest [AESI] and the Serious Adverse Events [SAEs]. The auditor subsequently requested the Clinical Team to conduct Source Data Verification [SDV] of more patients at this site and it was decided in the weekly team interaction meetings that PPD will send three CRAs to this site who will attempt to monitor 100 randomly selected subjects spread out among the 407 subjects enrolled. On the monitoring visit on February 18, 19 and 21, 2002 the three PPD CRAs Ann-Marie Cisneros, Elizabeth Heding and Stephanie Love monitored 36 subjects (Elizabeth Heding and Stephanie Love monitored only on February 18 and 19, 2002 and Ann-Marie Cisneros monitored on all three days).

ATTACHMENT 1

GCP-QA was informed by e-mail on February 27, 2002 by Jessica Lasley, Director TCC, PPD, about the observations of the CRAs of potential scientific misconduct discovered during the interim monitoring visit, which took place at the site of Dr. Anne Kirkman-Campbell [Investigator No. 1129] on February 18, 19 and 21, 2002 (the clinic was closed on February 20, 2002).

First elements received reported that proper diagnosis of an appropriate medical condition to warrant study entry was lacking; medical charts were very limited; short time of randomization in the IVRS (large numbers of patients in a short increment of time and most occurred when the office was closed for lunch and not seeing patients); informed consent form anomalies including date modifications and patient signature inconsistencies; and a review of lab values for multiple patients appeared to be similar. At the time of the monitoring visit, Dr. Kirkman-Campbell site had enrolled 407 patients.

In accordance with the applicable Aventis Global Regulatory SOP GREGU-QAC-PR-01-01 "Scientific Misconduct and Fraud", a teleconference was organized on March 4, 2002 to review the case, and evaluate first investigations to be initiated.

Main points discussed and actions agreed upon are listed below.

Issues Notified

1. Review of lab values for multiple patients apparently similar:

   John Reynolds (CRA, TCC, PPD) observed that on several occasions the lab samples sent to Covance on the same day had similar patterns of results for two or more subjects. W. Stager (Statistician, Aventis) made a related observation that the intraday variance of the lab samples sent by Dr. Anne Kirkman-Campbell is considerably less than the interday variance of her samples. These observations together led to the suspicion that blood samples may not have originated from unique subjects. Further statistical analysis is planned to investigate this hypothesis.

2. Review of the elements regarding informed consent form and patient informed consent obtaining process:

   As per Ann Marie Cisneros, Sr. CRA, PPD the following issues were observed with informed consent:

   - Subject 249/ Informed Consent signature for the Subject does not resemble the signature in the Subject's medical chart dated 10/13/97.
   - Subject 361 Initials on each Informed Consent page differ from page to page and do not resemble the Subject's signature.
   - Subject 388/ Initials on each Informed Consent page differ from page to page and do not resemble the Subject's signature.
   - Subject 335/ Initials on each Informed Consent page differ from page to page and do not resemble the Subject's signature.
   - Subject 333/ Initials on each Informed Consent page differ from the Subject's signature. The date of signature was changed from 1/17/02 to 1/18/02 and 'verified' by the subject, however, the initials do not match the subject's signature.

3. Source Documentation Issues:

As per Ann Marie Cisneros, Sr. CRA, PPD the following issues were observed with Source Documents:

- Subject 361/ The Subject's medical chart consisted of 3 total pages. One page had the Visit 1 and 2 dates the subject was seen for the TREAT study, another page had the study drug given to the subject and one page was totally blank.
- Subject 333/ the day of Visit 1 was changed from 1/17/02 to 01/18/02 on only one page of the 2 page medical chart. The subject was being seen for follow up on hypertension. In different ink "sinus congestion x2 days" was added. (See informed consent issue for this subject above).
- Subject 272/ Subject was randomized in the IVRS and the day of Visit 1 on the CRF occurred on 1/16/02, however the consent was signed and blood sent in on 01/09/02. The subject's medical chart does not indicate a visit on 1/9/02, however the subject had labs drawn (not study related) on 01/08/02. In the medical chart there is documentation of a visit occurring on 01/08/02, however that date was changed to 1/16/02. It is apparent the subject did not date their signature on page 6 of the ICF. The lab results from 01/08/02 are similar to those sent in to Covance on 01/09/02. Labs were not sent in on 1/16/02.
- Subject 077 Subject was seen on 11/30/01 for feet and ankle swelling. In a different pen, "chest congestion x3days" was marked on the form and Acute Exacerbation of Chronic Bronchitis indicated. The subject's physical exam, respiratory section, respiration were even and unlabored, clear/equal sounds bilaterally, lung fields no flatness, dullness or hyperresonance. The subject does not have a history of bronchitis.
- Subject 405/ he day of Visit 1 was the first day the subject was seen in the office. Chief complaint was back pain, in different ink in the middle of the medical history page, "chest congestion 2-3 days" was written in. The subject did not have a history of Chronic Bronchitis, or any respiratory problems.
- Subjects 312, 361, 344, 355, 300, 263, 223, 196, 359, 407, 405, 393, 188, 161, 135, 077, 063 were diagnosed with AECB, however had no documentation of past history of bronchitis.

Ann Marie Cisneros, Sr. CRA, PPD confirmed that valid source documents existed for the subjects reviewed. The progress notes contained diet charts, medical charts and patient information sheets in most instances.

4. Time of randomization in the IVRS:

The time of randomization in the IVRS is very short between several subjects randomized (large numbers of patients in a short increment of time and most occur when the office was closed for lunch and not seeing patients).

Investigation Plan

In the light of the elements collected, further investigation was deemed necessary.

Actions: Recommendation was given to carefully follow up the implementation of the following actions:

W. Stager (Statistician, Aventis) will perform a statistical analysis of the lab data from Covance to determine the likelihood of obtaining the observed numbers of matching lab samples by chance.

The Study Manager will ensure that a follow up letter is sent to the site asking for written explanation of the following issues by the site:

- A description of the informed consent process and an explanation of the issues observed.
- It is understood that the nature and extent of the disease state is not critical to this clinical trial mimicking normal practice but the PI should explain the source documentation practices followed by the site and clarify the issues observed in the monitoring visit.
- The randomization of subjects in blocks/ clusters within a short period of time is highly unusual. The site should explain the randomization process followed by them.
- Having reported very few Adverse Events (except for the five AESIs consisting of abnormal Liver Function Tests) for the 407 subjects enrolled is highly unusual. What is the process at the site for obtaining and documenting Adverse Events from subjects?

This follow up letter will not discuss the issue of the lab values for multiple patients appearing to be similar and the informed consent issue of Subject 249 . Aventis GCP-QA will review this follow up letter before it is sent to the site to ensure that all outstanding issues have been addressed and appropriate follow up has been requested.

Since the monitoring plan requires a monitoring of 25% patients and until now source data verification for only 49 of the 407 subjects has been performed [3 in the monitoring visit on November 29, 2001, 10 during the Clinical QA Audit on January 17-18, 2002, and 36 during the monitoring visit on February 18, 19 and 21, 2002] the possibility of a further monitoring visit will be explored. This is necessary to rule out the possibility of any unreported Adverse Events of Special Interest [AESIs].

The answer will be obtained from the site to the question asked in the Audit Follow up letter dated January 21, 2002 about the total number of patients seen by the PI in the months of October, November and December 2001.

Documentation will be obtained from PPD about the training given to the site regarding the complete definition and reporting

	requirements of Adverse Events of Special Interest [AESI] and the Serious Adverse Events [SAEs]. Based upon the statistical analysis of the lab data from Covance and the responses of the PI to the follow up letter, meeting will be held to decide future action.